diac source of increased circulating concentrations of cardiac troponin T" by Jaffe et al. (2) published in the October 2011 issue of the *Journal*. In their letter, Sribhen et al. (1) share their experience on a case of a 27-year-old man experiencing severe rhabdomyolysis after abdominal surgery due to intestinal herniation with bowel gangrene. Initially, this patient showed a concordant increase in the third-generation cardiac troponin T (cTnT) and cTnI assays on the third post-operative day with a consecutive fall in cTnT and cTnI levels. Subsequently, the cTnI level decreased to reference ranges, whereas the cTnT level began to rise again, reaching a maximum on the 18th post-operative day. Based on the report of Jaffe et al. (2), the researchers argued that these findings support the hypothesis that the re-elevation of the cTnT level might be the consequence of re-expression of cTnT isoforms in skeletal muscle during the subacute phase of rhabdomyolysis. In support of their hypothesis, the researchers argued that a higher rate of elevations in cTnT level as compared with cTnI level is also found in end-stage renal disease (3) and quoted reports on cross-reactivity of the first-generation TnT assay (4).

In our view, this interpretation is neither substantiated by their data nor the data provided by Jaffe et al. (2) in the original paper or his comments accompanying this letter.

First, extensive testing during development of the cTnT assay showed no false positive cTnT elevations, even in patients with severe skeletal muscle injury and extremely high blood creatine kinase activity.

Second, in the particular patient reported by Sribhen et al. (1), there are many possible reasons for elevations in cTnT and cTnI levels on the third post-operative day, such as post-operative myocardial infarction, acute renal failure, systemic inflammatory response syndrome due to intestinal gangrene, and pulmonary embolism, to name only a few. These established causes of troponin release are—in our opinion—a much more likely explanation for the cTnT elevations than re-expression of cTnT isoforms in skeletal muscle. There have been no scientific data yet indicating re-expression of cTnT in skeletal muscle in severely diseased patients in the intensive care setting.

Third, the reasons for the discordant findings of cTnI and cTnT are unclear, and the limited clinical information provided by Sribhen et al. (1) does not contribute to clarification. Several factors may interfere with the cTnI measurements, causing a false negative result, such as hemolysis, heparin interference, autoantibodies, heterophilic antibodies, and a lower analytical sensitivity and precision of the third-generation cTnI versus cTnT assay (5).

The observation of cTnT, and less often cTnI, elevations in some patients with skeletal muscle myopathy or dystrophy is interesting and most likely explained by myocardial involvement due to a systemic disorder. Nevertheless, the possibility of re-expression of cTnT in skeletal muscle merits thorough scientific evaluation. However, the study cohort reported by Jaffe et al. (2), which is used in support of the case, is subject to an inherent inclusion bias because only those patients who were cTnI negative but cTnT positive were included in the trial. So far, no data are available in an unselected population with skeletal muscle diseases. In their paper published in the *Journal*, Jaffe et al. (2) concluded that they found the "same molecular weight proteins in diseased skeletal muscle and in the heart." However, looking closer at the figures revealed that immunoreactive proteins in the diseased skeletal muscle detected by Western blotting had a different molecular weight as compared with cTnT in heart muscle (Fig. 2 of their article). For the soleus muscle extract, 2 peptides were heavily stained using the monoclonal cTnT antibody M7, and these peptides had molecular weights much lower than cTnT (Fig. 3 of their article). Interestingly, the skeletal muscle samples were not probed for cTnI re-expression. Thus, it is impossible to prove the re-expression of troponin T in skeletal muscle by these experiments. Only sequencing of the proteins that were stained by the antibodies in the Western blot would clarify if indeed a cTnT fragment or much more likely unspecific binding of the antibodies in tissue sections could explain the staining in the Western blot.

We believe that interpretation of elevated cTn concentrations, particularly when more sensitive assays are used, has become a challenging task for clinicians. However, the case by Sribhen et al. (1) and the explanations provided by Jaffe et al. (2) are not substantiated by robust scientific data and therefore will not aid in explaining the TnT elevations in this complex case.

There is a large database indicating that elevation of cTns in the absence of acute coronary syndrome, commonly mislabeled as a false-positive cTn result, is an independent predictor of patient outcome, particularly if myocardial damage is due to a different mechanism than myocardial ischemia. Thus, so far there are no robust scientific data supporting the hypothesis that re-expression of cTnT in skeletal muscle may be a reasonable explanation for elevated TnT levels in critical care.

***Evangelos Giannitsis, MD**
Hugo A. Katus, MD

*Department of Cardiology
University of Heidelberg
Abteilung Innere Medizin III
Medizinische Klinik
Heidelberg, Baden Württemberg 69120
Germany
E-mail: evangelos.giannitsis@med.uni-heidelberg.de

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Reply

We thank Drs. Giannitis and Katus for their interest in our paper (1) concerning the clinical specificity of cardiac troponin T (cTnT)

in skeletal muscle disease. Because several parts of their letter also referred to the article by Jaffe et al. (2), which is beyond the scope of our discussion, we will respond only to the parts addressing the results of our study.

Drs. Giannitis and Katus have stated that the re-elevations of cTnT found in the subacute phase (2 to 4 weeks) of rhabdomyolysis in our patient could be due to post-operative myocardial infarction or pulmonary embolism. However, the patterns of cTnT release that showed chronic elevations, and not acute rise and fall, over several weeks are not typical of acute ischemic events. They also stated that the negative cardiac troponin I (cTnI) results observed in our study might occur as a result of interference by certain factors present in the blood samples. In this regard, it is true that analytic interferences by hemolysis or heterophilic antibodies may cause false-negative troponin I results (2). Nevertheless, these interferences can occur in both cardiac troponin assays. In addition, it is unlikely that hemolysis caused negative troponin I results in all 5 blood samples that were measured in the subacute phase of rhabdomyolysis. Furthermore, why should the interfering effects of heterophilic antibodies occur only in the subacute phase and not in the acute phase in blood samples obtained from the same person?

To substantiate the significance of our findings, we report another patient with chronic renal failure who was receiving maintenance hemodialysis and developed rhabdomyolysis after limb ischemia. As in the first index case, there were significant increases in both creatine kinase myocardial band and cTnT (third-generation immunoassay; Roche Diagnostics, Basel, Switzerland) from elevated baseline concentrations during the second to fourth weeks of the acute event, with peak values of approximately 7-fold the upper limit of reference ranges (personal observation). During this period, no increase in cTnI (first-generation immunoassay; Ortho Clinical Diagnostics, Raritan, New Jersey) serum concentration was observed. Of interest was the observation by Visvanathan and Visvanathan (3), who reported a female patient with sepsis-associated rhabdomyolysis exhibiting persistent elevations of cTnT and creatine kinase myocardial band serum concentrations throughout her stay in the rehabilitation unit of more than 2 months. Unfortunately, measurement of cTnI was not performed. Nonetheless, the authors theorized that the prolonged elevations of cTnT were most likely due to reexpression of the cTnT isoform in regenerating skeletal muscle.

In this context, it should be noted that we did not intend to provide evidence for the reexpression phenomenon with data from our case study. Rather, the results are hypothesis generating and, in agreement with Drs. Giannitis and Katus, require thorough scientific evaluation and confirmation from large studies.

Kosit Sribhen, MD
***Nilrat Wannasilp, MD**
Rewat Phankingthongkum, MD

*Clinical Pathology
Faculty of Medicine, Siriraj Hospital
Mahidol University
Bangkok 10600
Thailand
E-mail: nilrat_w@hotmail.com

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Multidetector Computed Tomography for Detecting Lesions That Are at High Risk for Myocardial Necrosis After Percutaneous Coronary Intervention

Watabe et al. (1) should be commended for their recent study, which evaluated the impact of coronary plaque composition on cardiac troponin elevation after percutaneous coronary intervention in patients with stable angina pectoris. It is a novel approach and could have important clinical implications. However, a few pertinent points should be considered before reaching a final conclusion. First, multidetector computed tomography (MDCT) has some serious limitations when used for plaque analyses, including and not limited to, overestimates of plaque volume (especially for calcified plaques), limited ability to identify thin-cap fibroatheromas (vulnerable plaques) due to limited spatial resolution, and a very high interobserver variation in plaque assessment (2,3). Most of the studies supporting the ability of MDCT to differentiate culprit and nonculprit lesions are retrospective and have their own limitations; moreover, the significance of individual plaque characterization has been challenged in a large-scale prospective study (4).

Second, although soft and fibrous plaques cannot be distinguished on the basis of computed tomography attenuation, other features of plaque vulnerability, such as "ring-like enhancement" on MDCT, have been described (5); it would be interesting to know if the authors made an attempt to study and include such features in the current study (1).

Third, difficulties in delineating vessel borders and poor image quality, especially in obese patients, are other practical aspects that limit MDCT utility. These limitations, along with the fact that the current study included only Japanese patients (1), who usually have lower body mass indices than the typical Western patient, further limit its direct clinical applicability to Western populations.

***Abhishek Sharma, MD**

*Maimonides Medical Center
1016 50th Street
Brooklyn, New York 11219
E-mail: abhisheksharma4mamc@gmail.com

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